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**Aerobic exercise, cognitive behavioural therapy and energy conservation
management for Multiple Sclerosis (MS) fatigue: Are three trials better than one?**

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This edition of Multiple Sclerosis Journal includes reports from three randomised controlled trials (RCTs) of cognitive behaviour therapy¹, aerobic training² and energy conservation³ management for the treatment of MS fatigue. The three trials were led by separate research teams as part of the Dutch TREFAMS-ACE consortium⁴. Each trial compared one of the active treatments against a standardised control condition of three 45-minute individual face-to-face consultations with experienced and trained MS-nurses over a 4-month period. The MS nurses gave patients a standardised brochure about fatigue. Patients had the opportunity to discuss their fatigue and set goals for managing fatigue. In contrast, the three active treatments (summarised in the Table) included 12 45 minute individual face-to face treatment sessions with a health professional over the same time period. Participants in all three trials were followed up over 12-months. The primary outcomes, Checklist Individual Strengths (CIS20r)⁵ domain fatigue and Impact on Participation and Autonomy Questionnaire (IPA) ⁶ were identical in all studies. Secondary outcomes included the Modified Fatigue Impact Scale⁷ and the Fatigue Severity Scale⁸. ECM showed no significant improvements over the control condition on any outcomes. The CBT and aerobic training RCTS reported positive effects on the primary and secondary fatigue measures at the end of treatment, but effects were lost at 52-weeks follow-up. None of the trials found a positive effect for the active interventions on IPA at any follow-up point.

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The three trials have addressed several limitations prevalent in many RCTs of interventions for MS fatigue conducted to date, particularly exercise interventions ⁹. Multiple therapists have been included in each active arm making the results more

generalizable. Attention has been paid to assessing treatment fidelity, measuring treatment compliance, and collecting serious adverse events. This makes it easy to determine that the active treatment interventions studied here are acceptable to patients and safe to administer, as reported adherence rates were high and adverse events low (none directly linked to the interventions themselves). Further confirmation of acceptability can be inferred from the reports of drop-out during the intervention. This varied across the interventions with 7 out of 43 (16%) for exercise, 2 out of 44 for CBT (5%) and 8 out of 42 for EC (19%), suggesting the CBT treatment protocol may be the most acceptable intervention. .

Risk of bias has been minimised through concealed random allocation to treatment arms, assessors were blind to treatment arm allocation, and most patients were followed up even where they had dropped out of treatment. Furthermore, the studies provide good examples of clear and transparent reporting. The studies were registered with ISRCTN and the protocol published⁴. The trials are written following CONSORT guidelines¹⁰ and detailed descriptive data across all time points are presented in the appendices. The treatments in each arm are clearly described using TiDier guidance for describing complex interventions¹¹.

Despite these strengths, these trials do have some limitations. One is the trials are open to attrition bias¹². The percentage of data lost to follow-up and final analysis is summarised in the Table. The CBT and exercise RCTs lost substantially more participants from the control group than the experimental group at long term follow up. The ECM study excluded some participants from the final ITT analysis. These weaknesses could

have been partly addressed by including a treatment effect sensitivity analysis for attrition. In addition, to provide a clearer picture of the subsample not included in the analysis, it would have been useful to see baseline characteristics of the participants for whom data have been analysed versus those lost to follow-up ¹².

We are also unconvinced by the need to design three RCTS rather one. The TREFAMS group argued that three RCTs each recruiting from two separate centres would minimise contamination across treatment arms⁴. Whilst this may be logistically simpler, randomising 137 of 266 patients overall to control arms with only between 42 and 44 people per trial randomised to active interventions is an inefficient design. With one large trial, a greater proportion of patients could have been randomised to active treatments providing greater power to detect treatment effects across interventions. Furthermore, while recruiting 266 patients to three studies is no small task, we have concerns about the power of the studies to detect important differences.

The power calculations for the three studies accounted for 10% attrition rather than 20% attrition as stated in the papers. Based on 20% attrition, sample sizes should have been 50 per-group rather than 45. A bigger issue is that the studies were not powered to detect appropriate effect sizes. The studies were powered to detect an 8-point difference on the CIS20R (SMD=0.63), which whilst being 'clinically significant', will likely be considerably larger than the minimum clinically important difference (MCID). We could find no published MCID for the CIS20R. However, for other fatigue measures, MCIDs are typically in the order of SMDs between .3 and .4.¹³ The studies were also not explicitly powered to detect effects on the co-primary IPA outcome or any of the secondary outcomes. IPA is a general measure of quality of engagement in societal roles which can be influenced by a

wide range of general and MS related factors other than fatigue, and as such one would expect smaller effects. Underpowered studies lead to a higher risk of false negative results and as such limit inferences that can be drawn from the studies. Non-significant effects simply indicate that there is insufficient evidence to reject the null hypothesis, not that we can infer no treatment effect exists.

Perhaps most importantly, without one large RCT, we cannot draw direct inferences about the three treatments approaches. This is disappointing as to date, no trials have attempted to explore the relative efficacy of these three approaches. To have a better understanding of how the findings across these three trials compare, we have converted the treatment effects reported for the CIS20R fatigue measure to standardised mean differences (SMD) and plotted these out against time below (see figure). Negative values favour the intervention. All three interventions show some effect in favour of the intervention at 16-weeks (but this is non-significant for the ECM group). None are significant by 26 weeks, although the effect size for CBT is still moderate. None of the interventions show any effect after one year.

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We have also used these SMDs to conduct a multivariate meta-analysis using a fixed effect model, which allows for the estimation of the uncertainty around the differences in effect sizes across the three studies ¹⁴. Bearing in mind this is indirect evidence, we have made some cautious inferences with respect to the different effects across studies. The effect size for CBT compared to ECM is SMD=0.57 (95% CI: -.05 to 1.19) in favour of CBT

and compared to exercise is $SMD=0.22$ (95% CI: $-.38$ to $.82$) in favour of CBT. For exercise compared to ECM, $SMD=0.35$ (95% CI: $-.27$ to $.97$). The confidence intervals provide further evidence that compared to CBT and aerobic exercise, ECM is unlikely to be efficacious. However, there is less certainty to draw firm conclusions about CBT compared to aerobic exercise. Obviously, there are just three studies here and a proper network meta-analysis is needed, including all published studies.

Although we cannot use this indirect evidence to draw firm conclusions about the interventions studied, it helps to inform the design of future RCTs in this area. ECM appears to have a small effect size at best (further limited by dropout) so is not worth further research on its own, particularly as there are now several EC studies showing small or null effects¹⁵. Future trials could use ECM as a better and more matched control condition for either exercise or CBT. We also need to focus on how to maintain treatment effects in an illness where increasing disability, fluctuating symptoms and relapse are likely. This may mean longer term treatments or booster treatment sessions. Perhaps combining CBT and exercise would provide greater benefits. We also need more mechanistic studies of fatigue in MS to design more optimal approaches.

Future studies also need to be considerably larger than the three reported here. Power calculations need to account for larger attrition and number of primary outcomes. The TREFAMS-ACE protocol suggests there may be secondary papers from these three trials exploring possible mechanisms of the treatment effects. Whilst these future papers may be informative in terms of next steps, these trials are not well powered for mediation and moderation analyses. Large trials with clearly embedded process analyses will help us to refine and personalise treatments¹⁶.

Future RCTS in this area also need to be more pragmatic and consider broader generalisability. These three trials were largely efficacy trials. Patients with high Hospital Anxiety and Depression Scale¹⁷ scores were excluded. Although this makes sense in trying to rule out the possibility of the effects of depression on fatigue, it limits the generalisability of findings. In addition, the patients in these three RCTs had low mean disability scores (Expanded Disability Status Scale)¹⁸ and the majority had relapsing remitting MS (see Table). Fatigue occurs across the board in MS and effective interventions are needed for people with higher levels of disability including reduced mobility.

Finally, implementation of these interventions in normal everyday health care needs to be more carefully considered. The CBT protocol here included 12 face-to-face sessions with an experienced CBT therapist. Bearing in mind effects were not sustained at long term follow-up, this is unlikely to be a cost-effective treatment. CBT therapists experienced in treating fatigue are also not readily available to most patients with MS fatigue. The exercise intervention included the provision of home training equipment, but only for the duration of the study and only one type of exercise. Any exercise program needs to consider how to embed exercise as a habitual part of an everyday lifestyle that can be sustained once the intervention is finished. To do this, exercise needs to consider personal preference (enjoyment) of type of exercise and tailoring of exercise during times of symptom fluctuation or more serious relapse.

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Table: Summary comparison of the three TREFAMS-ACE Randomised Controlled Trials

Study reference	N Demographic and Disease Factors Female (%); (RRMS (%); Age years M (SD) EDSS Level of disability Median (range) Time since diagnosis Median years (range)		Lost to end of treatment follow-up % (drop out + non- response)		Lost to 52-week follow up % (drop out + non- response) % Analysed in ITT		Summary of theory/ rationale behind treatment	Who delivered treatment (level of training)	Timing & Mode of Delivery (week x frequency x minutes (mode))
	Experimental	Control	Exp	Con	Exp	Con			
Cognitive Behavioural Therapy (CBT) van de Akker et al. 2017	n=44 Female: 71%, RRMS 73 % Age: 51 (8.3) EDSS: 3 (2.8- 3.6) MS length 8.2 (2.9 – 14.2)	n=47 Female: 83%, RRMS 75% Age: 46 (11.6) EDSS: 2.5 (2.3 -3.0) MS length 5.2 (2.1 – 11.5)	14%	22%	11% ITT 100%	26% 98%	Cognitive behavioural model of MS fatigue:-disease factors trigger fatigue in MS, and cognitive, emotional, and behavioural factors perpetuate the severity and impact of fatigue. CBT for MS fatigue aims to influence cognitions, behaviours and emotions that perpetuate fatigue.	6 CBT state-certified healthcare psychologists Received 3 day training in this protocol. Supervised every second week by a supervising CBT psychologist	12 x 45 minute (face-to-face) individual outpatient sessions over 16 weeks) Therapy tailored to patients' individual needs.
Aerobic exercise Hein et al., 2017	n=43 Female: 74%, RRMS: 73%; Age: 43 (9.8) EDSS: 2.5 (2.0- 3.5) MS length 7.0 (2.0 – 10.0)	n=46 Female: 72%, RRMS:74%; Age: 48 (9.2) EDSS: 3.0 (2.0-4.0) MS length 12.0 (2.0 – 19.0)	14%	19%	23% ITT 100%	35% 100%	Aerobic exercise may result in improvements through increased fitness, normalisation of hormonal functions, & changes in neuroinflammatory & neuroprotective biomarkers.	6 trained physiotherapists Experienced in treating MS patients. Specific trial intervention training not reported.	12 individually supervised 45 minute outpatient aerobic interval training sessions on Kettler x7 home trainer over 16 weeks Regular prescribed home exercise over 16 weeks on Kettler x7 home trainer provided for duration of study.
Energy Conservation Management (ECM) Blikman et al. 2017	n=42 Female: 81% RRMS: 76% Age: 48 (11.0) EDSS: 2.5 (2-4) MS length 6.5 (3.7-17.4)	n=44 Female: 68% RRMS 73% Age 47 (11.5) EDSS: 3 (2.8-3.6) MS length 7.5 (3-14)	14%	9%	19% ITT 88%	20% 91%	Aims to promote a positive attitude towards active decision-making and the optimum use of the available energy to fit the unique needs of individuals. ECM aims to reduce the impact and severity of fatigue, to increase patients' use of energy-conserving strategies and to improve their confidence in their ability to manage fatigue.	4 x occupational therapists familiar with MS & ECM & qualified in motivational interviewing Training included programme guideline and 1 day ECM refresher course	12 x 45 minute (face-to-face) individual sessions over 16 weeks Patients given an ECM workbook

Abbreviations: Cognitive Behavioural Therapy (CBT); CON (Nurse-led Control group); ECM (Energy Conservation Management); EDSS (Expanded Disability Status Scale); EXP (Experimental intervention group); RRMS (Relapse-Remitting Multiple Sclerosis).

Figure legend: Standardised mean differences for each intervention compared to control. Negative values favour intervention.

